THE NATIONAL CHILDREN'S STUDY

Opportunities for Linking Biomonitoring to Risk Assessment and Public Health in the National Children's Study

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Today's Presentation

- Overview of the National Children's Study (NCS)
  - Background
  - NCS Research Plan
  - Proposed Measures
- NCS and Risk Assessment
- NCS and Public Health

National Children's Study

- Largest long-term study of children's health and development ever to be conducted in the U.S.
  - Approximately 100,000 children to allow study of important but less common outcomes
- Longitudinal study of children, families, and their environment
  - From before/early pregnancy to age 21
- Environment defined broadly
  - Chemical, physical, behavioural, social, cultural
- A platform for children's environmental health research

Study Concepts

- Aims
  - Identify potential environmental effects: harmful, harmless, helpful
  - For important conditions and diseases of children, identify potential preventable causes
- Hypothesis driven
- Exposure begins with pregnancy
- Has power to study high priority conditions (n~100,000)
- Gene environment interaction
- National resource for future studies

Hypotheses Necessary for Framing the Study

- Assure answers to “big issue” questions
- Hypothesis required for costly elements
- Input from >2500 scientists, others
- Important for child health & development
- Requires and measurable with sample ~100,000
- Evolving with the science
- Updated hypothesis statements in Research Plan

Priority Exposures and Health Outcomes

Priority Exposures	Examples
Physical Environment	Housing quality, neighborhood
Chemical Exposures	Pesticides, phthalates, metals, air & water quality
Biologic Environment	Infectious agents, endotoxins, diet
Genetics	Interaction between environmental factors and genes
Psychosocial milieu	Families, SES, institutions, social networks

Priority Health Outcomes	Examples
Pregnancy Outcomes	Preterm, Birth defects
Neuro-development & Behavior	Autism, schizophrenia, learning disabilities
Injury	Head trauma, Injuries requiring hospitalizations
Asthma	Asthma incidence and exacerbation
Obesity & Physical Development	Obesity, Diabetes, altered puberty

Time Line for the NCS

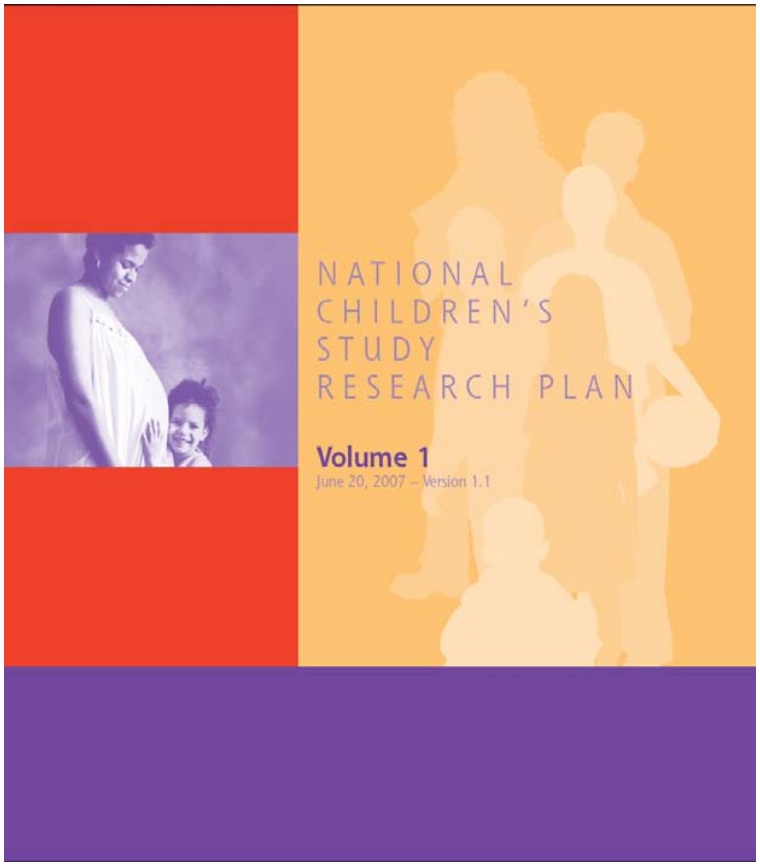
2000-present	Pilot studies/methods development
2004	Developed Study Design and Study Plan; Posted Requests For Proposals: Coordinating and Vanguard Centers
2005	Awarded initial contracts (Coordinating and Vanguard Centers)
2007	Completion of the first phase of the Study protocol
2007	Award Wave I Study Center contracts
2008	Reviews and approvals (OMB, Peer review, IRB's)
2008*	Repository and Laboratory procurements
2008-2009*	Additional Center and Location procurements (wave 2&3)
2008-2009*	Begin pilot cohort at Vanguard Centers (VCs)
2009-2014*	Begin full Study at VCs and additional Centers
2010*	First Study results become available (methods, pilots, preliminary findings)
2015*	Full data set for outcomes of pregnancy

*Pending funding

Funding for the NCS
(as of April 2007)

- FY 2000-06: ~ $50m from existing budgets of NICHD/EPA/CDC/NIEHS
  - Infrastructure: Study Plan; Coordinating Center and 7 Vanguard Study Centers…
  - Scientific development: 30 workshops, 20 scientific reviews, 19 pilot studies; hypotheses, exposure and outcome measures, protocol in progress…
- FY 2007: **$69m appropriated February 14**
  - Prepare for recruitment and enrollment at VG Centers
  - Develop Information Management System
  - Establish additional centers for expanded locations toward full sample
- To conduct the full Study: FY ’08-’34 ~ $3 B

The NCS Research Plan

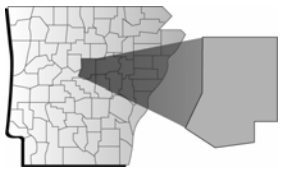


- The background, design and measures to describe what will be done and why.
- Designed for review
- 600+ pages
- On the NCS website: www.nationalchildrensstudy.gov

Study Sample

All Births in the Nation

~4 million births in 3,141 counties



Sample of Study Locations

105 Locations

Sample of Study Segments

Selection of neighborhoods

Study Households

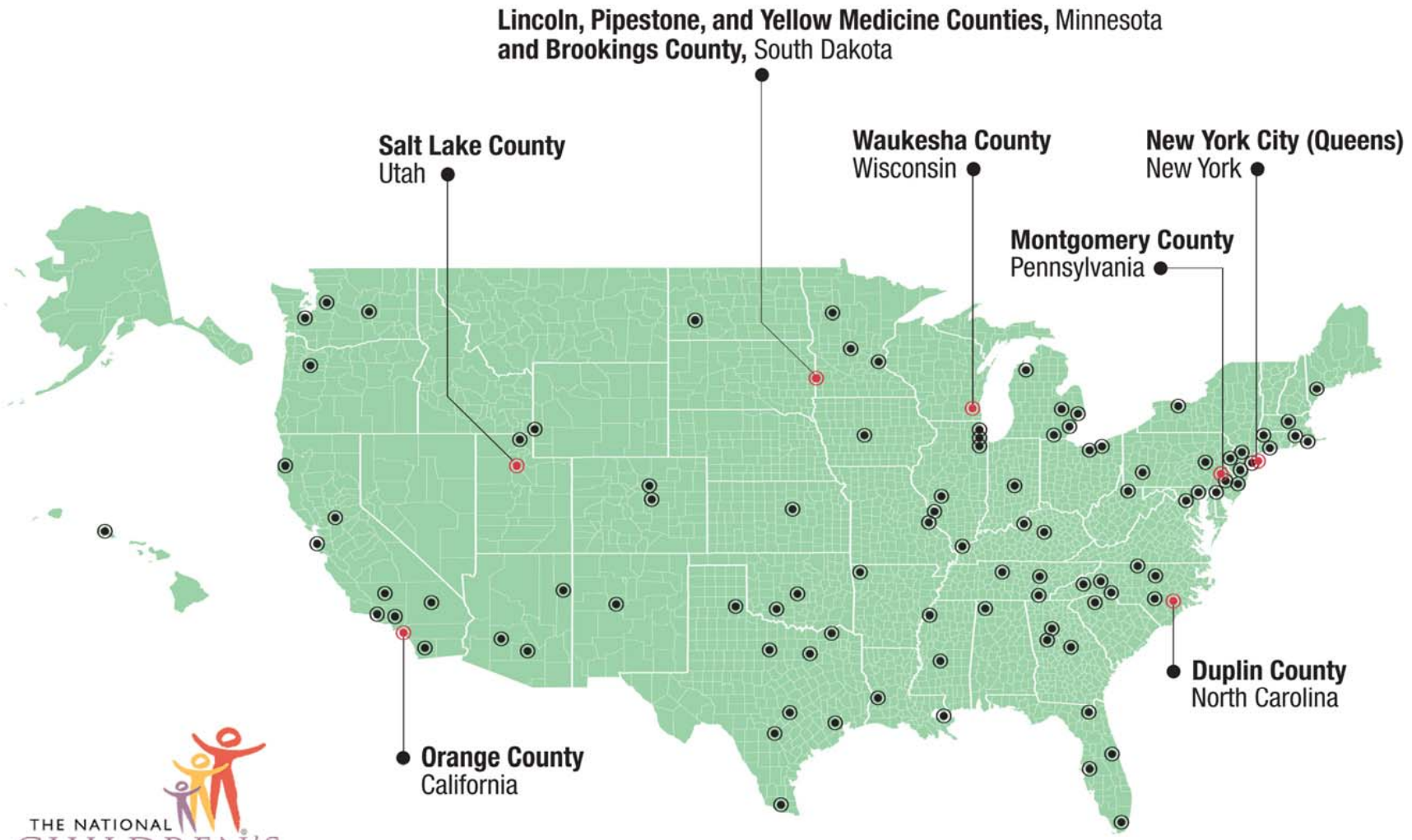
All or a sample of households within neighborhoods

Study Women

All eligible women in the household

National Children's Study Locations

Vanguard locations: Study Centers awarded (bold)



February 2006

Schedule of Visits

- 13 face-to-face contacts over the 21 year study period
- Contacts most frequent early in the study
- Between visits ongoing data collection by phone, mail, etc.

Home

Clinic

To be determined

Note: Frequency and type of follow-up for women (first 4 yrs) depends on their probability of becoming pregnant

1st Trimester	5 years
2nd Trimester – Study Ultrasound	7 years
3rd Trimester	9 years
Birth – Place of delivery	12 years
6 months	16 years
12 months	20 years
3 years	

Hypotheses->
Target Chemicals,
Routes, Life-Stage

Indirect Measures
(e.g., Community)
or Questionnaires?

Environmental & Biomonitoring?	Environmental?	Biomonitoring?
Importance of Route	Biomarker not available	Route of exposure not important
Time represented by environ. & biological	Route of exposure is critical	Biomarker reflects exposure over critical life stage(s)
Completeness of combined environ. & biological measures	Exposures can be more reliably/efficiently assesses using environ.	Exposures more reliably assessed using a biomarker

Based on Ozkaynak, et.al., “Exposure Assessment Implications for the Design and Implementation of the National Children’s Study” *Environmental Health Perspectives 113: Aug. 2005*

Proposed “Core” Environmental Measurements

Indoor Air (Residence, Child care locations)	Particulate Matter (PM_{10}) NO2, O3, VOCs, Aldehydes and Ketones
Outdoor Air (Community-level)	$PM_{2.5}$ NO_2, NO_x, SO2, O3
House Dust	Allergens, endotoxin, mold, metals, pesticides (+archive for future analyses)
Potable water	Disinfection byproducts (BBPs), Metals, Coliforms, Nitrate, Pesticides
Soil & Food	Metals, pesticides

Proposed Biomonitoring for Chemical Agents

Blood	PCBs, Persistent and non-persistent pesiticides, PBDE, Perfluorinated compounds, PBDE flame retardant; Perchlorate; Lead, Mercury, Cadmium; Bisphenol A
Urine	PFBS, Alkyl phenols, Hg(inorganic), As(speciated), perchlorate, halogenated phenols (PCP), phthalates, atrazine, OPs, carbamates, pyrethroids, EBDC/ETU, Cadmium
Breast milk	Dioxins/furans; Organochlorine Pesticides; PCBs
Meconium	Cotinine, Organophosphate Metabolites
Nails	Mercury (organic, inorganic)
Hair	Cd, Cotinine, Mercury, Nicotine

Proposed Questionnaire Topic Areas in the NCS

Housing characteristics	Building age, renovations Heating/cooling systems/usage, Clothes dryer, Vaporizers, Air cleaners, Stove use, Water for drinking and cooking, Ozone sources, Vacuum cleaner use, Garage location and use, Gasoline exposure, Noise
Occupation/hobby	Types of jobs, activities, exposures
Product use	Creams/lotions that are widely applied; Cleaning products
Pesticide use	Type, method, frequency of application, and use protective equipment; Number and types of pets, and exposure to flea/tick treatments

Proposed Questionnaire, Diary, or Observation

Visual assessment	Housing, neighborhood characteristics
Time and activity	Time spent at home, work/school, in-transit for work and non-work days
Diet	Food-frequency questionnaire 3-day checklist Infant feeding/intake Eating behaviors (child)
Exposure-Related Topics	Environmental tobacco smoke Take home exposures Physical activity Household composition and demographics

Example Environmental Measures over Time

Simplified Summary of Measures by Visit - Environmental Measurements							
	Pre-	Pregnancy		After Birth			
		T1	T2/T3	6-Mo	12 mo	2-yr	3-yr
Indoor Air			(self)			(self)	(self)
PM10/metals, carbon							
Gaseous Air Pollutants							
House Dust							
Pesticides							
Metals (store)							
Allergens, Mold, Pollen							
Drinking Water							
Disinfection Byproducts (DBPs)							
Nitrate (private wells)							
Pesticides (private wells)							
Perchlorate (Community Level)							
Soil							
Mid-yard - Metal, Pesticide							
Others							
Visual Assessment							
Noise Survey							

Other Data Collections

- Community samples
  - Water
  - Air monitoring
  - Possibly food
- Specific settings outside of the home
  - Child care locations (probably on a subsample due to costs)
  - School (specifics not yet developed)
- Medical Record Abstraction
  - Complete abstraction of the mother and infant records at the time of delivery
  - Likely additional abstractions for a subset of events and/or outcomes

Design Considerations for Exposure Assessment in the NCS

- *Validation sampling* provides a statistical basis to adjust for error in exposure assessment when investigating exposure-outcome relationships
- A *validation sample* is a small sample designed to provide information on the bias or error introduced by using alternative measures [or models] of exposure
- Need to develop optimal designs and identify surrogate measures [, questionnaires, or models] and their relationship to "true" exposure

Strauss W, Lehman J, Morara M, Ryan L. 2003. Development of Exposure Assessment Study Design for the National Children's Study: Project Overview, Results and Recommendations. Task 5. US EPA, National Exposure Research Laboratory. Available as Appendix C from: http://nationalchildrensstudy.gov/research/analytic_reports/

Analytes (Environmental and Biologic)

- Collections and storage protocols based on analytes specified in the hypotheses
- Many analyses will be deferred
  - Too costly and not necessary to have every analysis on every participant
  - Many hypotheses can be addressed with nested case-control studies
- Limited set of analytes require immediate processing
  - Depends on stability of sample/analytes

THE NATIONAL CHILDREN'S STUDY

Opportunities for Linking Biomonitoring to Risk Assessment and Public Health

Biomonitoring and the National Children's Study

- Prime applications of biomarkers are epidemiological observational studies.
  - Relate biomarkers (at various times) to outcomes
- NCS requires and employs extensive use of biomarkers
  - Assays to test hypotheses
  - Repository of biological and environmental samples for future analyses and hypotheses
- Biomarker database - http://www.nationalchildrensstudy.gov/research/analytic_reports
- Evolving science and methodological developments = new improved measures & better science, e.g.:
  - EPA/NCER Early indicators of environmentally induced disease
  - NIEHS – Exposure biology Initiative

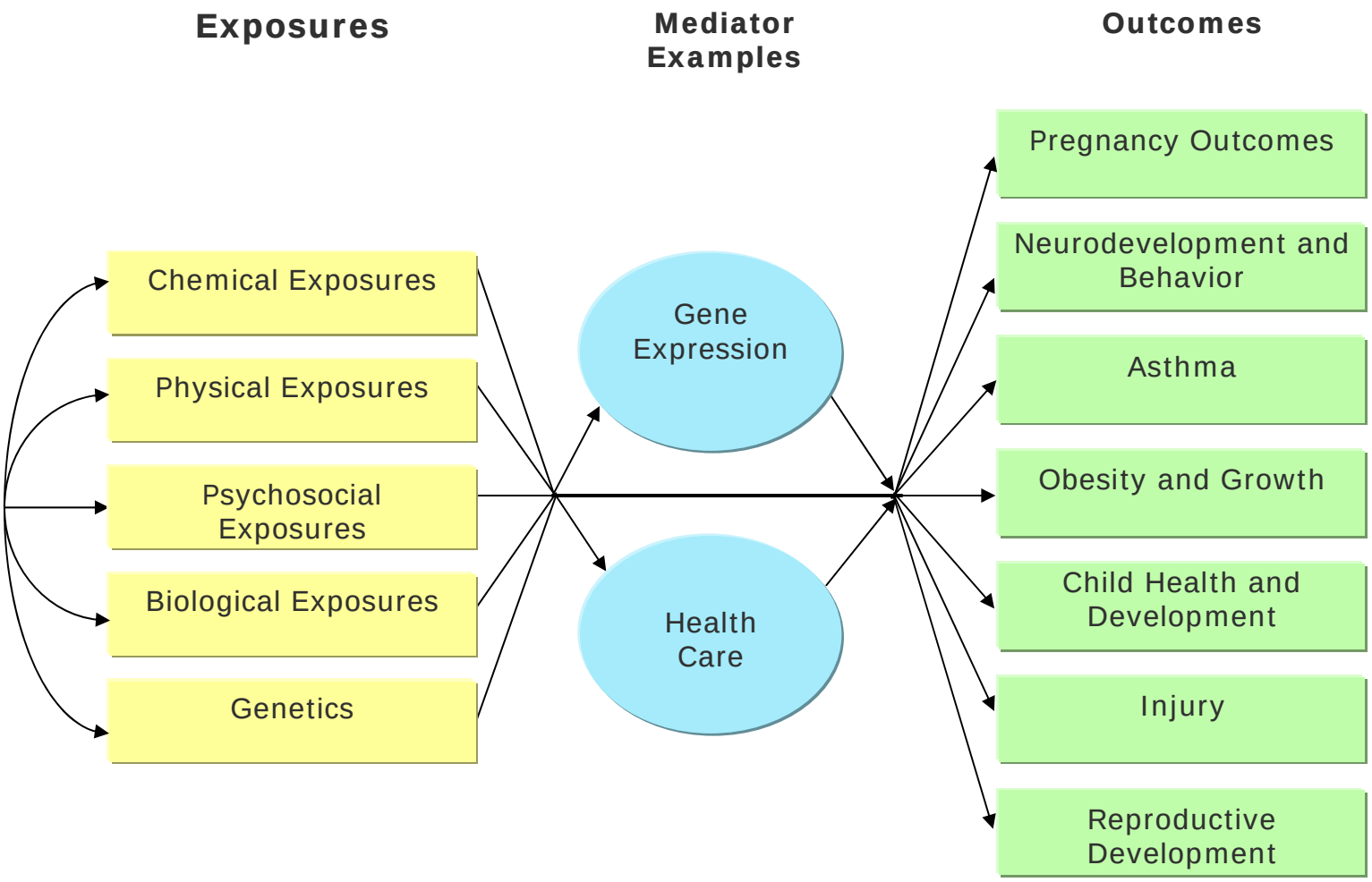
NCS and Risk Assessment

- NCS will address important issues for environmental risk assessment, such as:
  - Contribution of multiple exposures to childhood disease
  - Long-term health effects from early exposures
  - Factors that alter susceptibility (e.g., specific genetic polymorphisms, immune deficiencies)
  - Disparities in health outcomes (e.g., race, ethnicity, poverty, housing, income, nutrition)
  - Uncertainty factors and defaults in risk assessment for protecting children

NCA and Risk Assessment

- Directly links human exposure measures (biomonitoring and environmental) to health status, yielding better estimates for children, including the role of
  - Multiple “environments” and agents
  - Genetic factors and gene-environment interactions
- NCS will provide a rich data base for risk assessment, e.g.
  - Longitudinal exposure measures
  - Community-level cumulative risks

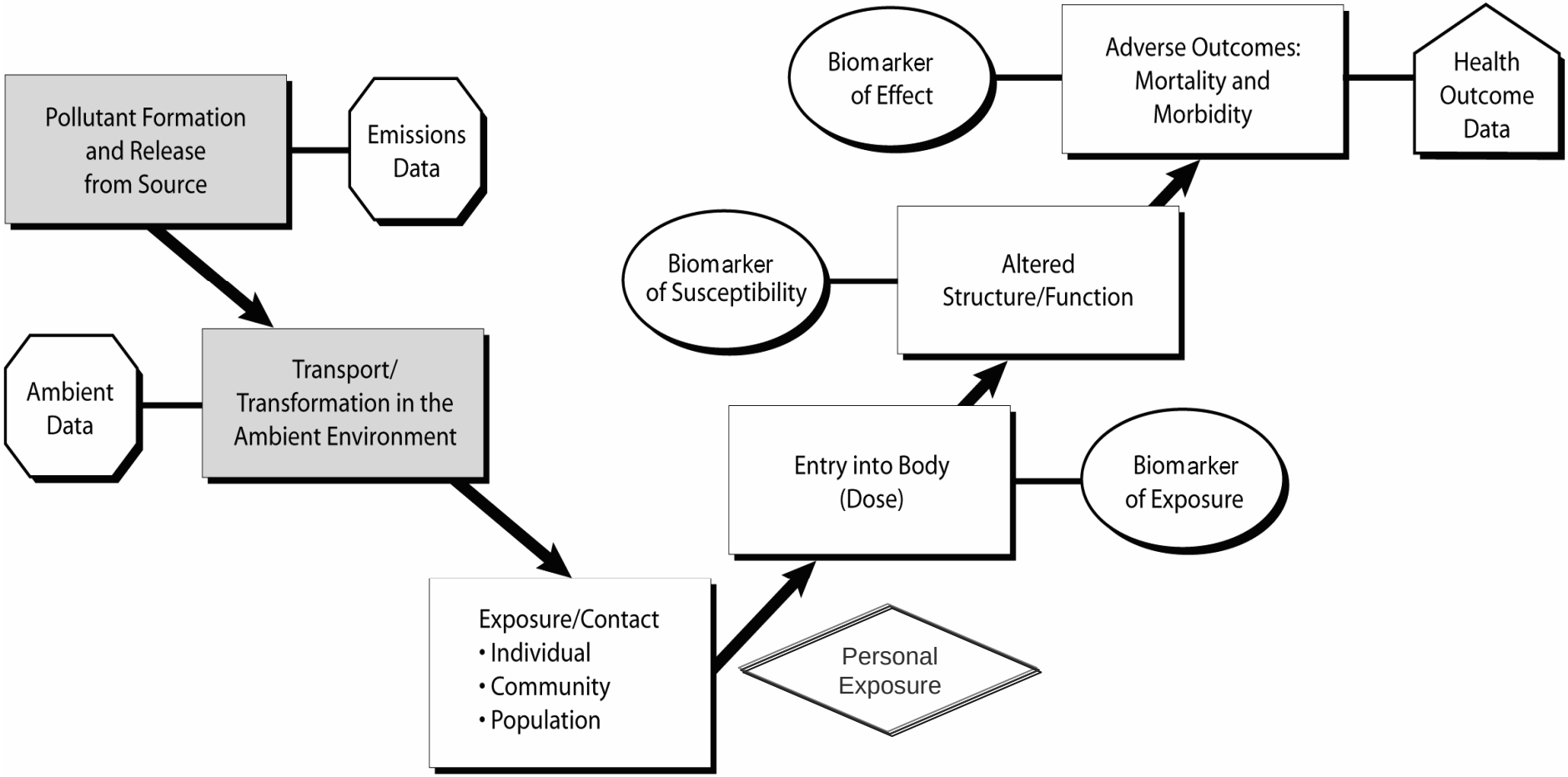
Conceptual Model: Exposures, Interactions, Mediators, and Outcomes



NCS and Public Health

- The NCS will identify not only what is harmful but what is helpful to children's health
- Provides a national dataset linking source-exposure-effect
  - Evidence on which to base decisions about practice and policy regarding children's physical and mental health
  - Allows evaluation of the consequences/effectiveness of regulatory decisions
- Economic benefits: disease prevention; cost avoidance
- Resource for future research

Environmental Public Health Paradigm



Source: Danelle T. Lobdell, US EPA, NHEERL

Environmental Indicators

Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Actions by EPA, State, and other regulatory agencies	Actions and behavioral changes by regulated community	Reduced amount or toxicity of emissions	Improved ambient conditions	Reduced exposure or body burden	Improved Human or ecological health

Data Available

Data Unavailable at present Time

Output Measures

Measures of Human/Eco- Health

NCS and Public Health Research

- Training for clinical, epidemiological, and environmental health research
- Consortia for combined research
- Pubic use and secondary data analysis
- Complimentary, not competitive, with investigator initiated research
- Platform for *adjunct studies*

What are *Adjunct Studies*?

- Uses NCS data, participants or their samples
- Outside of the “core” NCS protocol
- Generally supported with non-NCS funding
- NCS Program Office coordinates review and approval
- Requires participation of an NCS investigators
  - Study Centers, NCS Program Office, or ICC members
- Benefit of adjunct studies
  - Enhances breadth, depth and value of the NCS
  - Could use for linking biomonitoring and other exposure measures to sources

Use of Data to Maximize Output

- Publicly available results available ~2015
  - Hypothesis-specific (exposure-outcome) data analysis
  - Public-use data sets with support
- Successive funding for investigator initiated research and analyses
- Expected translation of results into related prevention initiatives
- Data analyses and adjunct studies may be needed
  - to link biomonitoring and exposure measures to sources

For more information about the NCS

Web site: www.nationalchildrensstudy.gov

Link on the home page that says “National Children’s Study Research Plan”

Click on link for “E-Updates” to join the listserv for news and communication

Email the study at ncs@mail.nih.gov